

# ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

Section Editor: Clifford A. Hudis, MD

## Breast Cancer In Focus

### Brain Metastases from Breast Cancer

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**H&O** Can you provide some background on metastatic disease in breast cancer?

**AS** We have long known that breast cancer can metastasize to the brain, and with recent improvements in systemic therapy that control metastases in sites such as the bone, liver, and lung, we now see patients living longer, which has allowed brain metastases that might have otherwise remained occult to manifest. We know from autopsy studies that brain metastases can be found in approximately 20–25% of women. Currently, approximately 10–15% of patients with a diagnosis of breast cancer may expect to have brain metastases, which certainly represents a clinical feature associated with a poor prognosis. Survival for patients with brain metastases is commonly measured in months and not years. We also recognize that there are specific molecular subtypes of breast cancer that seem to have a greater propensity for metastasis to the central nervous system, specifically the triple negative breast cancers—the estrogen-, progesterone-, and HER2 receptor–negative breast cancers—as well as breast cancers that overexpress HER2. In these subsets of cancer, brain metastasis can occur in approximately one-third of all patients.

**H&O** Do we know why specific subtypes of breast cancer metastasize more frequently to the brain than others?

**AS** On a molecular basis, we do not entirely know why some subtypes metastasize to the brain. There is

a tremendous amount of ongoing research that is trying to elucidate the molecular mechanisms that allow those subtypes of breast cancer to metastasize; I am currently working with a Department of Defense Breast Cancer Research Program group called The Center of Excellence, which is a consortium of basic scientists and clinical investigators. We have been working together for a number of years, both in the laboratory and clinic, to unravel some of the biologic underpinnings of these unique features.

**H&O** What are the treatment options for women with brain metastases from breast cancer?

**AS** Historically, we have mostly relied on whole brain radiation, which offers the convenience of treating the whole brain, not just some of the lesions that are present in the brain. Although whole brain radiation can be an effective procedure, it also can frequently cause cognitive dysfunction, and for women with breast cancer who are living many years after brain metastasis, this is certainly not a trivial side effect. Consequently, there has been much interest in localized radiation, such as stereotactic radiation, which targets a limited number of metastases (also known as gamma knife). Stereotactic radiation may represent a possible option for selected patients to avoid some of the toxicities associated with radiating the whole brain.

Despite the judicious use of stereotactic radiation, many patients will still progress in other sites and ultimately may require whole brain radiation. One of the questions that we hope to answer as part of the Center of Excellence research effort is whether we might be able to identify systemic agents that will cross the blood-brain barrier and the blood tumor barrier to prevent the outgrowth of new brain metastases. We have some promising lead molecules from preclinical experiments that we hope to translate into clinical trials in the near future.

Currently, we rely on neurosurgery for patients with solitary single metastasis or a limited number of metastases (up to 3); however, these lesions have to be in a favorable anatomic location in order for patients to undergo successful neurosurgical resection. A thorough knowledge of the neurologic map of the brain is necessary to determine if the lesions are in an area of the brain that would not be affected by surgery.

Systemic chemotherapy is another therapeutic option, albeit modestly effective. One area of investigation is whether systemic drug therapy has any value in controlling metastases that have progressed despite radiation; we have some evidence that such treatment can be effective. In the *Journal of Clinical Oncology*, Dr. Nancy Lin reported on the benefit of lapatinib (Tykerb, GlaxoSmithKline), an oral inhibitor of epidermal growth factor receptor (EGFR) and HER2, in patients with HER2-positive brain metastases. The drug seemed to have some penetration across the blood-brain barrier and some evidence of efficacy, but the duration of disease control was modest (2–3 months).

In breast cancers that are of any HER2 status, we have recently studied a novel epothilone called patupilone (Novartis). Data from studies of patupilone were presented at the American Society of Clinical Oncology meeting. In preclinical models, patupilone crossed the blood-brain barrier and has demonstrated evidence of benefit in patients whose brain metastases have progressed despite radiation. So far, however, I remain unimpressed because the efficacy that we have seen with these trials is modest at best.

Another research avenue that investigators at Baylor College of Medicine and Memorial Sloan-Kettering are pursuing is the use of anti-angiogenic agents concurrent with whole brain radiation. The group at Baylor is examining the use of sunitinib (Sutent, Pfizer) in combination with radiation. Here at Memorial Sloan-Kettering we plan to study the oral anti-VEGF and multi-tyrosine kinase sorafenib (Nexavar, Bayer) in combination with whole brain radiation.

The “Holy Grail” is the prevention of brain metastasis in the first place. Efforts to prevent the outgrowth of new metastasis in patients who have already developed brain metastasis may inform us on how to employ these strategies in appropriate high-risk patients even in the adjuvant setting. This would truly be a transformational approach to identifying those patients with early breast cancer who have a high likelihood of brain metastasis and employing a specific systemic agent that would reduce the chance of patients ever developing brain metastasis in the first place. This is where we all hope to be in the future, and that is indeed one of the focuses of the research efforts of the Department of Defense group.

**H&O** What kind of prognostic indicators would indicate that a patient has better odds at survival?

**AS** There have been numerous attempts at developing prognostic scales and indicators for breast cancer. One of the important issues is whether or not the patient’s non-central nervous system metastases are controlled. Performance status is also a good indicator. For example, if the patient is mostly bedridden due to fatigue and is limited by her disease, simply asking her about her daily activities can be a very useful indicator to predict longer-term survival. There have been other attempts to look at more complicated tools, but those have been mostly useful in patients with primary brain tumors, where the brain is the only site of disease. Generally, triple-negative status, which is more common in premenopausal and African American women, has been reported to be associated with a shorter survival in the presence of brain metastasis compared to HER2-positive status.

**H&O** What are the typical symptoms a patient with brain metastases may experience?

**AS** One of the symptoms is headache, which can be quite variable, depending upon the position of the tumor(s) in the brain. Some patients will describe early morning headaches, or sometimes headaches that are associated with nausea and vomiting. When patients describe something that is “the worst headache of their life,” it should absolutely prompt imaging for brain metastasis. Sometimes patients will have neurologic symptoms, such as a seizure or, depending upon the location of the lesion, weakness of an extremity, such as an arm or a leg, or speech impediment. If a lesion is in the cerebellum, it can manifest as trouble with balance and coordination. One of the most frightening things is that many brain metastases will be detected without any symptoms at all. Although this is worrisome, it allows doctors to be proactive and to intervene before neurologic symptoms or deficits develop.

Patients who present with headache or other neurologic symptoms described above usually are sent for a magnetic resonance imaging (MRI) scan. Computed tomography scanning can also detect some brain metastases, but it can also miss them and other manifestations of CNS disease, such as leptomeningeal disease, in which cancer cells may not have invaded the parenchyma of the brain tissue but are coating the meninges, which can also cause significant neurologic morbidity. In this circumstance, a lumbar puncture should be performed to look for metastatic cells in the cerebrospinal fluid.

The issue of imaging leads to the very important question of whether breast cancer patients should be screened. Should patients who are at any risk, or those

particularly at high-risk, like the triple-negative and the HER2-positive patients, receive an MRI every 6 months or so even in the absence of headaches and neurologic symptoms? Unfortunately, we do not have an answer to this question. At present, we lack prospective randomized studies comparing women assigned to brain MRIs as a screening test to those who are not.

I think that in scenarios where there is a 30–40% chance of developing brain metastases in triple negative and HER2-positive patients, getting a brain MRI preemptively to find lesions before they cause symptoms, whether it is every 6 months or once a year, could impact a patient's quality of life by reducing neurologic morbidity from breast cancer. Furthermore, the use of localized treatments like stereotactic radiation offers the opportunity to intervene in a fairly nontoxic way, where the treatment does not necessarily have to be worse than the disease.

### **H&O** Has there been any progress in studying the blood-brain barrier, and have any agents been developed that help increase its permeability?

**AS** We have long recognized that some drugs may penetrate the blood-brain barrier, yet we still see very little evidence that they are effective against brain metastasis. Drs. Patricia Steeg, Diane Palmieri, and Paul Lockman have conducted some very novel work in mouse models of breast cancer brain metastasis that have pointed to the blood tumor barrier as being important and distinct from the blood-brain barrier. In these studies, vascular remodeling and other molecules such as efflux transport proteins may have a role in making brain metastasis less vulnerable to systemic therapy. Also, our institution is in collaboration with our colleagues at the Cleveland Clinic to systematically measure inter-tumoral drug concentration in women who have a medical need to have a surgical resection of a brain metastasis or multiple brain metastases. We will be administering various drugs in the immediate preoperative period, which will allow us to determine whether the drugs are penetrating the tumors that are going to be resected at the time of surgery.

There are some researchers, such as Dr. Edward Neuwelt in Portland, Oregon, who have been championing the approach of blood-brain barrier disruption. There have been small pilot studies in which, for example,

mannitol is given to patients prior to the administration of chemotherapy to open up the blood-brain barrier in order to increase drug penetration. In some of those studies, chemotherapy is administered intra-arterially, not just intravenously; this approach requires a specialized team that is able to perform such procedures. Unfortunately, there have not been any controlled, randomized trials of this in breast cancer, and so this approach is still very investigational.

### **H&O** Have there been any advances in imaging techniques?

**AS** After patients are treated with whole brain radiation, in particular stereotactic radiation, it is hard to gauge how well the treatment worked. Patients are typically followed radiographically with MRI scans post radiation, and sometimes a tumor lesion will shrink, but then seems to grow. In some instances, that apparent growth does not represent progression of the cancer, but rather a phenomenon known as *radiation necrosis* or *radionecrosis*, which refers to dead tissue that causes swelling and edema and can masquerade as progression of cancer. Consequently, better imaging techniques are needed to differentiate viable tumor from dead tissue or necrotic tissue. Positron emission tomography has been examined for this, but seems to be limited in its ability to distinguish radionecrosis from progressive tumor. Another area of research that we are pursuing at our institution is studying the fluoro-L-thymidine (FLT)-PET, which is a novel radiotracer that we hope will be better at distinguishing live tissue from dead tissue.

### **Suggested Readings**

Anders CK, Deal AM, Khorram C, et al. The prognostic contribution of intrinsic breast cancer subtype, race, and age among patients with brain metastases. *J Clin Oncol*. 2010;28(15S):Abstract 1027.

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Palmieri D, Lockman PR, Thomas FC, et al. Vorinostat inhibits brain metastatic colonization in a model of triple-negative breast cancer and induces DNA double-strand breaks. *Cancer Res*. 2009;15:6148-6157.